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Myocarditis and Inflammatory Cardiomyopathy

Emanuele Bobbio and Kristjan Karason

Abstract

Activation of the inflammatory system occurs in most patients with advanced heart failure, regardless of etiology, and contributes to the pathophysiological milieu and the progression of the disease. The term *inflammatory cardiomyopathy* (ICM) refers to a group of disorders for which an acute or chronic myocardial inflammation is the central cause of abnormal cardiac structure or impaired cardiac function. The most common cause of inflammatory cardiomyopathy is *lymphocytic myocarditis*, which is most usually triggered by a viral infection, and occasionally by other infectious agents. Rare causes of specific inflammatory cardiomyopathies include *cardiac sarcoidosis*, *giant cell myocarditis* and *eosinophilic myocarditis*. Inflammatory cardiomyopathy can also occur in connection with autoimmune inflammatory diseases. Typical manifestations of inflammatory cardiomyopathy include chest pain, heart failure, and arrhythmias, but these symptoms and signs are unspecific. Although non-invasive diagnostic methods are emerging, the gold standard of diagnosis is the histological examination of an endomyocardial biopsy. Owing to the invasive nature of this technique and a modest diagnostic sensitivity, its use is limited. Therefore, the identification of inflammatory cardiomyopathy is elusive and the true incidence of the condition remains unknown. In most cases of lymphocytic myocarditis, recovery occurs within a few weeks following supportive treatment. In patients with cardiac sarcoidosis, giant cell myocarditis or eosinophilic myocarditis the use of immunosuppressive treatment is recommended, as is the case in myocarditis associated with autoimmune disorders. Such interventions may also have beneficial effects in chronic viral myocarditis once the virus has been cleared. In severe cases, treatment with mechanical circulatory support and/or heart transplantation may be required. Randomized intervention trials including antiviral, immunomodulating, or immunosuppressive agents are lacking. Similarly, new molecular-based methods and therapies tailored to specific pathogeneses have a potential to improve diagnosis and outcomes in patients with inflammatory cardiomyopathy. Still, such techniques and interventions are to be evaluated in adequate randomized controlled studies.

Keywords: myocarditis, inflammatory cardiomyopathy, lymphocytic myocarditis, cardiac sarcoidosis, giant cell myocarditis, eosinophilic myocarditis, heart failure, endomyocardial biopsy

1. Introduction

Myocarditis implies the presence of diffuse or focal inflammation in the cardiac muscle [1]. Although inflammation of the myocardium can be induced by

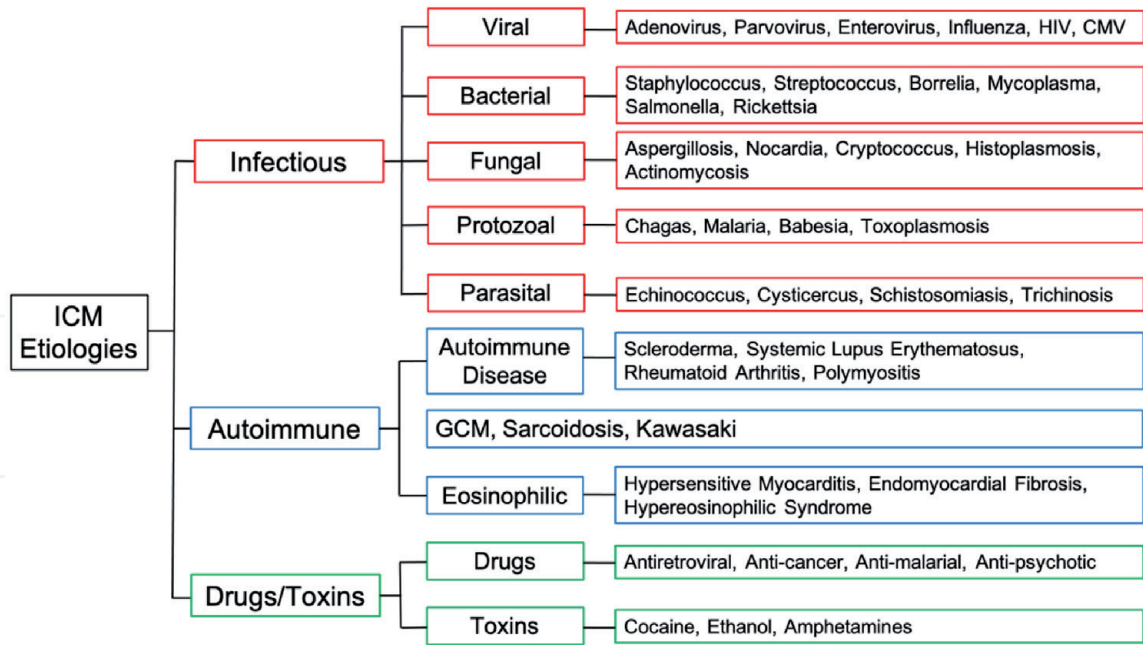


Figure 1.
Inflammatory cardiomyopathy (ICM) refers to a broad group of disorders for which inflammation of the myocardium represents the principal cause of ventricular remodeling and cardiac dysfunction.

a wide variety of autoimmune disorders, hypersensitivity reactions and toxins, the predominant etiopathogenetic factor is infectious agents; these are mostly viral, but can also include bacterial and protozoal microbes [1, 2]. Still, in the individual case the etiology can be difficult to identify. Inflammatory cardiomyopathy refers to a broad group of disorders for which inflammation of the myocardium represents the principal cause of ventricular remodeling and cardiac dysfunction (**Figure 1**) [3, 4]. This term is rather unspecific since as several cardiomyopathies a low degree of inflammation is present and an infectious agent can seldom be identified [1]. In contrast to hereditary cardiomyopathies, no monogenetic diseases cause inflammatory cardiomyopathy, although a genetic predisposition towards cardiotropic viruses and/or autoimmune reactions may occur in certain individuals [2, 5].

Myocarditis and inflammatory cardiomyopathy can be acute, subacute, or chronic [1]. The incidence and prevalence of these conditions are difficult to estimate as many cases are asymptomatic [2, 6] and the diagnosis is seldom verified with an endomyocardial biopsy (EMB) [7]. Nevertheless, myocarditis and inflammatory cardiomyopathy are noteworthy conditions related to poor outcomes, especially when complicated by heart failure and ventricular arrhythmias [5, 8]. This chapter will focus on cardiomyopathies associated with impaired cardiac structure and function for which inflammation is the primary cause.

2. Myocarditis and inflammatory cardiomyopathy

The previous histopathological diagnosis of myocarditis has traditionally been defined according to the Dallas criteria of 1986, which requires the presence of inflammatory cell infiltrates in the myocardial tissue and advocate classification into active forms with myocytolysis and borderline forms without cell necrosis [1, 5]. A histological diagnosis requires an endomyocardial biopsy, which is not only

resource-intensive, but also invasive with attendant potential for complications [9]. The Dallas criteria represented the first attempt to develop standardized diagnostic guidelines for the histopathological classification of myocarditis [10]. However, the practical use of these criteria is limited by their low sensitivity owing to variation in collection of the samples and inter-observer variability between different pathologists [7, 11].

In addition to histological examination, an endomyocardial biopsy can be examined with polymerase chain reaction (PCR) techniques to screen for cardiotropic viruses and with immunohistochemical methods to detect low-grade inflammation [1]. The value of these analyses is still unclear, however, as the results do not provide a clear guide with respect to the management and prognosis of inflammatory cardiomyopathy. For these reasons, many practitioners refrain from obtaining endomyocardial biopsies, with the result that myocarditis often becomes an exclusion diagnosis based on clinical features and other clinical examinations [1].

Cardiac magnetic resonance (MR) has been used more extensively in recent years to diagnose and exclude myocarditis and inflammatory cardiomyopathy (**Figure 2A**) [12]. The 'Lake Louise criteria', a consensus guide to cardiac MR in myocardial inflammation were published in 2009 [13]. These criteria focused on three diagnostic targets in the myocardial tissue derived from a signal intensity assessment in T2-weighted images with early and late gadolinium enhancement: 1) edema; 2) hyperemia; and 3) necrosis or scar. A high likelihood of myocarditis is assumed to occur if two out of these three criteria are positive [13]. The Lake Louise Criteria have subsequently been widely used in both clinical and research settings.

¹⁸Ffluoro-deoxy-glucose (FDG) positron emission tomography/computed tomography (PET/CT) is emerging as a diagnostic tool for the assessment of myocarditis and inflammatory cardiomyopathy (**Figure 2B**) [14]. As the activation of inflammatory cells is associated with increased glucose utilization, [15] myocarditis can be detected by PET after intravenous administration of FDG. The CT is added to identify the localization of myocardial inflammation, which correlates anatomically with increased glucose turnover. As compared with cardiac MR,

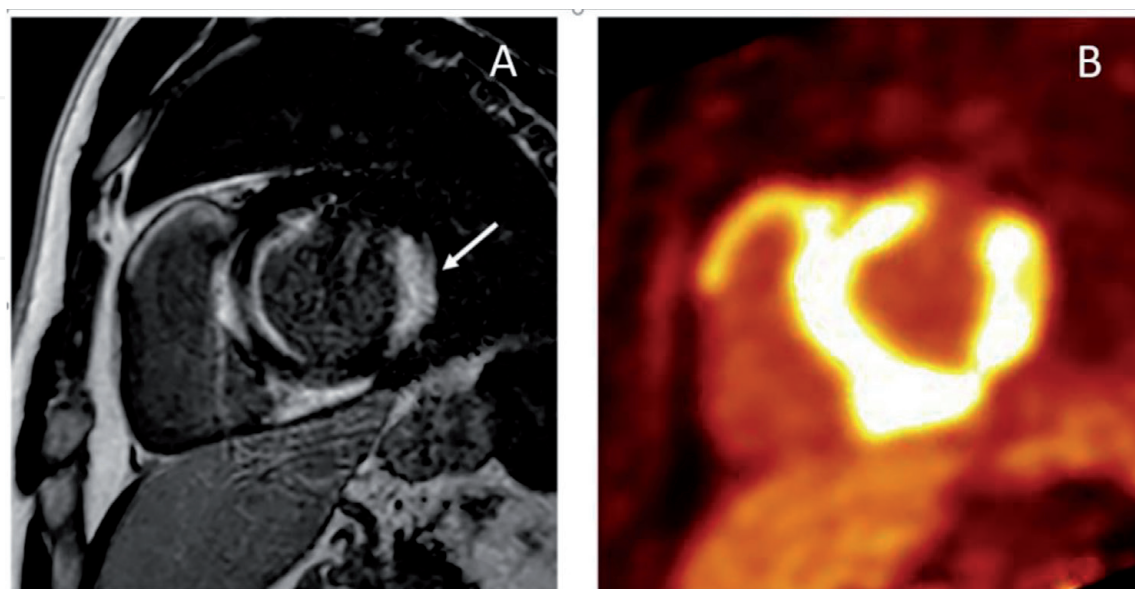


Figure 2.
 Images from a patient with cardiac sarcoidosis: A) cardiac MR (T2-weighted image) showing delayed enhancement (arrow) indicating inflammation and B) PET/CT displaying a general increase in glucose uptake in the cardiac muscle also indicating inflammation. Figure courtesy of Dr. Christian Polte.

PET/CT is associated with reduced radiation exposure, and demonstrates higher sensitivity of for mild or borderline myocarditis, and increased specificity for chronic myocarditis [14].

3. Etiology

Cardiotropic viruses are the commonest causes of myocarditis in Europe and North America [2]. The most frequently-encountered etiological agents include enterovirus (Coxsackie B virus), adenovirus and parvovirus. Other viruses that are sometimes detected include influenza virus, hepatitis C virus, and HIV. The spirochete bacterium, *Borrelia burgdorferi*, may in rare cases cause myocarditis, which mainly affects the cardiac electrical system resulting in atrioventricular (AV) block [2, 5].

Chagas' disease (American trypanosomiasis) is prevalent various countries of Central-and South America. The infection is caused by *Trypanosoma cruzi*, which is a protozoan parasite transmitted to humans by various species of triatomine bugs [16]. *Trypanosoma cruzi* can cause both acute myocarditis and a chronic inflammation leading to severe cardiomyopathy and advanced heart failure [16].

Myocarditis can also occur in connection with autoimmune diseases, mainly systemic lupus erythematosus, systemic sclerosis, and rheumatoid arthritis. Various pharmaceuticals and chemicals can cause myocarditis via a toxic or allergic reaction affecting the heart. Radiation, heat stroke and hypothermia are examples of physical injuries that have been associated with cardiac inflammation [1, 2].

4. Pathophysiology

The pathophysiological mechanisms of lymphocytic myocarditis have been studied in animal models for Coxsackie B virus and other cardiotropic viruses [17]. Coxsackie B virus, which is an RNA virus, is incorporated into the myocyte via a receptor and mediated endocytosis, after which virus replication occurs in the cytoplasm [2, 18]. Following toxic cell necrosis, the virus particles come into contact with the myocardial interstitial tissue and trigger an innate immune response. The myocardial tissue becomes infiltrated by macrophages and natural killer (NK) cells, which eliminate infected myocytes and produce several cytokines, including virus-inhibiting interferon and tumor necrosis factor- α (TNF- α), a cardio-depressant [2]. Over time, the adaptive immune system is also stimulated, leading to recruitment of cytotoxic T-cells and neutralizing antibodies that contribute to viral clearance. An experimental form of viral myocarditis has been proposed to cause cardiomyopathy through three different mechanisms (**Figure 3**) [2].

1. Adequate immune activation leads to healing of the myocarditis within two to three weeks, but the damage is so extensive that a clinical phenotype of dilated cardiomyopathy arises [18].
2. An upregulated and overactive immune response may cause tissue damage through infiltrations of T-cells and autoantibodies (autoimmune cardiomyopathy).
3. A downregulated and ineffective immune response can lead to continuous apoptosis through a persistence virus infection (viral cardiomyopathy) [1].

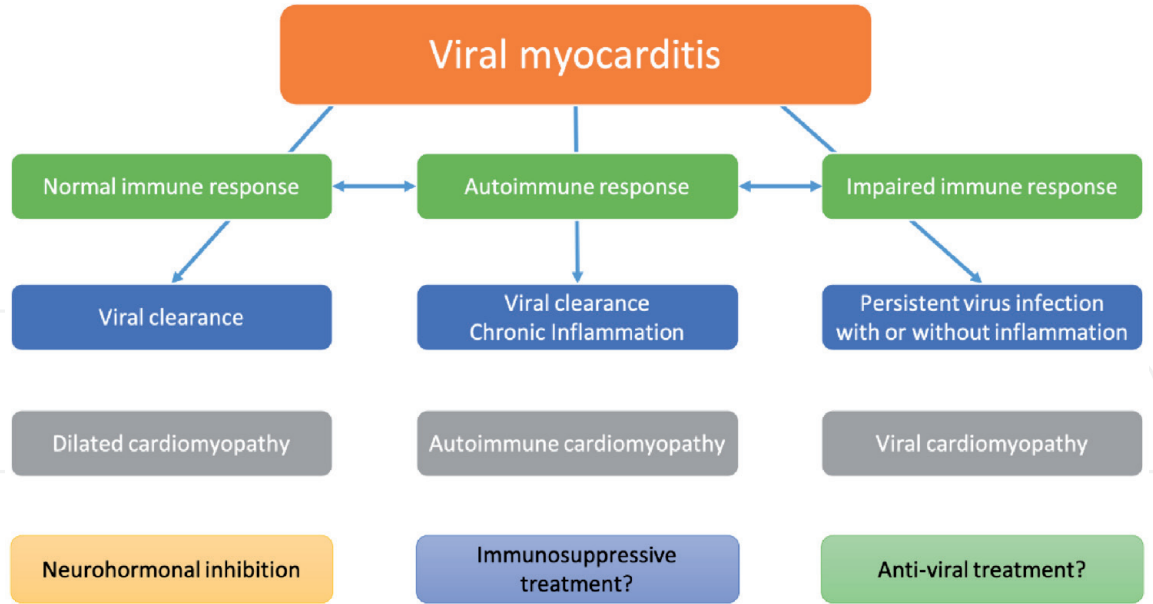


Figure 3.
An experimental form of viral myocarditis has been proposed to cause cardiomyopathy through three different mechanisms.

Findings that support the relationship between cardiotropic viruses and the development of cardiomyopathy in human studies include disturbances of T-cell regulation, inadequate expression of human leucocyte antigens (HLA) expressed and the presence of autoantibodies against cardiac epitopes [2].

5. Clinical features

Patients with myocarditis or inflammatory cardiomyopathy may present with a wide variety of symptoms and signs. The spectrum ranges from asymptomatic patients with minor changes on the electrocardiogram (ECG), or echocardiogram, to patients with fatigue, breathlessness, and palpitations and syncope due to impaired cardiac function or arrhythmias, and finally to patients with circulatory shock as a consequence of fulminant heart failure [19]. In some cases, the clinical presentation is preceded by influenza symptoms, upper respiratory tract infection or gastrointestinal discomfort, but in many cases, there are no prodromal symptoms [8].

Despite a large heterogeneity of the clinical picture, a few distinct forms can be identified.

1. Acute lymphocytic myocarditis presents with chest symptoms, comprising discomfort, pain, or palpitations, often combined with fatigue or breathlessness [19]. Fever and signs of infection can accompany the symptoms and myocardial biomarkers are frequently elevated. The ECG shows ST-T changes or arrhythmias and an echocardiogram can show regional hypokinesia or impaired systolic function [20]. The most usual differential diagnosis is acute coronary syndrome, which in most cases requires an exclusionary coronary angiogram. The treatment is mainly supportive (**Figure 4A**).
2. Fulminant myocarditis is an unusual but a very serious condition [6, 21]. The patient presents with cardiogenic shock including hypotension, tachycardia, and anuria without any other explanation for heart failure [22].

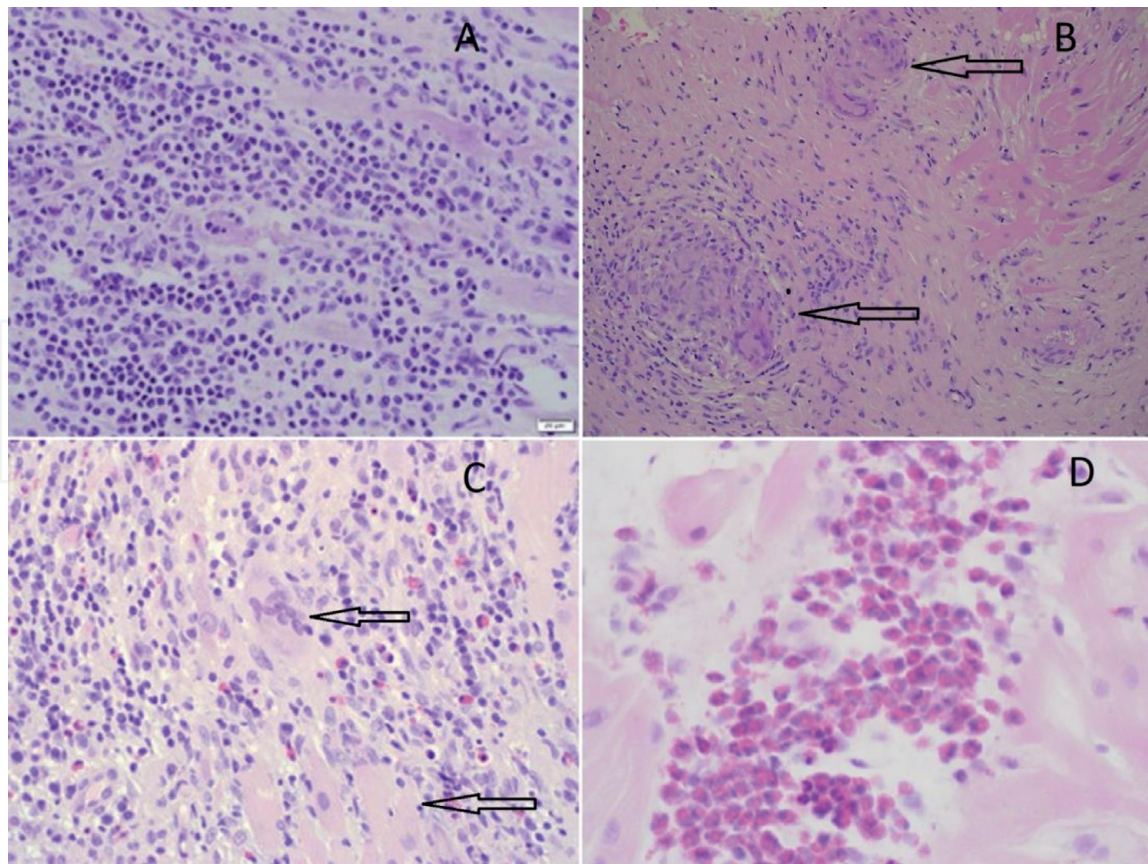


Figure 4. Histopathological findings on endomyocardial biopsies from patients with inflammatory cardiomyopathy (tissue-staining with hematoxylin and eosin). A) Lymphocytic myocarditis. Dense lymphocytic cell infiltration with some residual cardiomyocytes. B) Cardiac sarcoidosis. Non-caseating epithelioid cell granulomas (arrows) and fibrosis. C) Giant cell myocarditis. Widespread myocardial lesions with degenerated and necrotic cardiomyocytes and infiltration of mononuclear inflammatory cells, giant multinuclear cells (arrow) and some eosinophils. D) Eosinophilic myocarditis. Massive interstitial eosinophilic cell infiltration. Figure courtesy of prof. Anders Oldfors.

The echocardiogram displays poor ventricular contractility without dilation and a myocardial biopsy can be normal or show a varying degree of inflammation [22]. Such patients often require intensive care, with administration of an inotropic and/or vasoconstrictive drug and, in some case short-term mechanical circulatory support (MCS) [4]. The pronounced ventricular failure frequently recovers within a few weeks. It has been speculated that the temporary cardio-depressive feature can be caused by an extensive storm of toxic cytokines, which would explain why the myocardial biopsy can be normal [21].

3. Cardiac sarcoidosis, giant cell myocarditis and eosinophilic myocarditis are examples of three additional clinical entities, which will be discussed separately below.

6. Diagnostics

Laboratory analysis often reveals elevation of inflammatory activity and increases in circulating markers of myocardial injury, such as creatine kinase (CK) and troponin [8]. Elevation of natriuretic peptides indicates overt heart failure.

Virus serology is seldom conclusive. An ECG can show unspecific ST-T changes, T-wave inversions, AV block or tachyarrhythmia [20]. An echocardiogram can detect regional hypokinesia, as well as ventricular dilation and reduced ejection fraction [23]. A suspicion of myocarditis most often arises after a coronary angiogram has excluded an underlying coronary artery disease.

Cardiac MR is used for the workup of suspected myocarditis. With delayed enhancement techniques, general or focal accumulation of contrast can be seen, which differs from ischemic injuries and can be of value when deciding the localization of an endomyocardial biopsy [24]. The Lake Louise criteria can be applied to evaluate the likelihood for myocardial inflammation. A PET/CT that shows increased focal or general myocardial uptake of FDG supports the diagnosis.

An endomyocardial biopsy should be considered when acute or chronic heart failure of unclear genesis presents, as well as in patients with impaired left ventricular function of unknown etiology with contemporary arrhythmias of ventricular origin or a significant AV block [9]. If myocarditis is diagnosed this will influence treatment and determine the prognosis. Even if a myocardial biopsy is limited by suboptimal sensitivity and some risk, this investigation still serves as a pivotal tool for diagnosis of myocardial inflammation [7].

7. Treatment

Treatment of myocarditis and inflammatory cardiomyopathy is mainly supportive and conforms with standard medical therapy for other dilated cardiomyopathies [6]. Patients should receive conventional, guideline-directed medical heart failure treatment including beta-blockers, inhibition of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme (ACE) inhibitors or an angiotensin-receptor blocker (ARB), or as applied more recently, valsartan/sacubitril (an ARB combined with a neprilysin inhibitor [ARNI]), as well as a mineral corticoid antagonist (spironolactone or eplerenone) [25]. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are emerging as a new oral new therapy for heart failure patients who have reduced ejection fraction and are added to conventional therapy for patients both with or without diabetes [26, 27]. Loop diuretics should be added in patients who show signs of fluid retention [28]. If necessary, anti-arrhythmic therapy involving a pacemaker (PM) and/or an implantable cardioverter defibrillator (ICD) is indicated [6]. With severe heart failure, inotropic support may be necessary, or alternatively a short-term MCS [22]. The role of immunosuppression in myocarditis is controversial and its use as a general strategy is not advocated [29, 30].

Persons with acute myocarditis and mild myocardial infection frequently recover without any sequelae, but should refrain from heavy physical activity or sporting for at least 3 months due to an increased risk of ventricular arrhythmias [4].

8. Cardiac sarcoidosis

Sarcoidosis is a multisystem inflammatory disease of unknown etiology characterized by the presence of mononuclear phagocytes and non-caseating granuloma in different organ systems [31]. Although clinical heart disease has been confirmed in around 5% of patients with systemic sarcoidosis, up to 25% of such patients display signs of cardiac sarcoidosis at autopsy, indicating asymptomatic cardiac disease [32, 33].

The incidence of cardiac involvement varies between different ethnic groups: for example cardiac sarcoidosis is much more common among Japanese patients and African Americans than Caucasians [31]. A pronounced myocardial fibrosis can lead to a mixed picture of restrictive and dilated cardiomyopathy. The conduction system is more often affected in cardiac sarcoidosis than in other inflammatory cardiomyopathies, possibly due to an inflammation that is located in the atrium and the antero-septal wall of the left ventricle, which frequently leads to AV block [34, 35]. Granuloma formation can occur in all parts of the heart, but the cardiac valves and coronary arteries are usually spared [31]. The pericardium may also be involved, and pericardial fluid is present in 5-15% of cases [31].

It has been suggested that the incidence of cardiac sarcoidosis is increasing [36]. In the US, the incidence of transplant patients with cardiac sarcoidosis as their underlying condition increased from 0.1% to 0.5% between 1994 and 2014 [37]. Similar trends were reported from a Finnish nationwide cohort study [36]. However, this increase in incidence may be due to a progress in imaging techniques, increasing awareness and more aggressive diagnostics involving endomyocardial biopsies [36].

8.1 Etiology

Sarcoidosis is an inflammatory disease whose pathogenesis and inciting events are not well understood. Accumulating evidence suggests that the disease is caused by an immunological response to an antigenic trigger of unknown origin in genetically susceptible individuals [38]. Supportive of this are alleles of the *HLA-DRB1* locus, which are more common in patients with sarcoidosis [39]. In addition, exposure to environmental triggers and to various micro-organisms have been linked to the development of the disease [40].

8.2 Pathophysiology

Non-caseating granulomas are the histopathological hallmark of cardiac sarcoidosis (**Figure 4B**). The granuloma consists of a tightly packed follicle made up of lymphocytes (in particular CD4+ T cells), giant cells and epithelioid cells surrounded by a rim of fibroblasts and lymphocytes [41].

Clinical features of cardiac sarcoidosis depend on the location, extent, and activity of the disease. Cardiac sarcoidosis can also occur without clinical manifestations [31], but common symptoms include palpitations, dizziness and/or fainting [36]. Symptomatic cardiac sarcoidosis is a potentially serious condition that can lead to heart failure, life-threatening arrhythmias, and sudden death [42, 43].

8.3 Diagnostics

Emergence of symptoms and signs of heart disease in patients with known extracardiac sarcoidosis, especially young individuals with electrical conduction disturbances, should raise the suspicion of cardiac sarcoidosis. A careful history should be obtained with respect to palpitations, syncope and pre-syncope [31, 44]. An ECG may reveal unspecific ST-T changes, T-inversions, conduction disturbances or ventricular arrhythmias. Long-term electrocardiography can provide valuable additional information in the form of the numbers of both supraventricular and ventricular premature extra-systoles and supraventricular and ventricular tachyarrhythmias [45]. In clinically silent cardiac sarcoidosis, the echocardiogram is often normal, but with manifest disease, structural and functional aberrations become apparent [45, 46]. Those defects are variable and usually non-specific, although inter-ventricular thinning, especially basal, left and/or right ventricle diastolic and systolic

dysfunction, and isolated wall motion abnormalities, may indicate cardiac sarcoidosis [31]. Cardiac MR, and to an increasing extent FDG-PET/CT, are today considered to be the best methods for detecting and visualizing sarcoidosis in the heart muscle [31]. Both techniques can visualize active inflammation (**Figure 2**) [47–49]. Although the pattern of late gadolinium enhancement on Cardiac MR is usually patchy and multifocal, with sparing of the endocardial border, this is neither specific nor diagnostic for cardiac sarcoidosis [50, 51]. An endomyocardial biopsy that displays non-caseating granulomas strongly supports the diagnosis, but is not pathognomonic.

In patients with extra-cardiac sarcoidosis, a lymph node or lung biopsy is typically preferred to endomyocardial biopsy because of the lesser procedural risk and higher diagnostic yield [36, 48]. However, in the case of a negative extra-cardiac biopsy, an endomyocardial biopsy may be required. Nevertheless, owing to the patchy distribution of the disease, and endomyocardial biopsy reveals non-caseating granulomas in less than 25% of patients [52].

8.4 Treatment

A strong suspicion of cardiac sarcoidosis motivates treatment with high dose corticosteroids with slow tapering. Studies have shown regression of high-grade AV block after corticosteroid treatment, as well as a reduced frequency of ventricular arrhythmias in the acute phase of the disease [53]. Most patients - but not all - benefit from this treatment. Methotrexate is also an option, but is mainly given to facilitate tapering of steroids and, thus, alleviate their side effects [31]. The optimal treatment period for corticosteroids is still debated, but should not be less than one year and, in most cases, should be longer. If a decision is made to end corticosteroid treatment, it is important to follow the patient closely for possible relapse, especially during the first year [36].

Antiarrhythmic drugs usually have only a limited effect on rhythm disturbances in patients with cardiac sarcoidosis. Beta-blockers are the first choice for both supraventricular and ventricular arrhythmias [53] and amiodarone can be tested in acute situations with ventricular tachycardia (VT). If the arrhythmia events are associated with active inflammation, corticosteroids should be added or their dose increased. If satisfactory results are not achieved, VT ablation may be considered [34, 35]. Class I anti-arrhythmic agents are not recommended in patients with cardiac sarcoidosis as most patients have structural myocardial changes in the form of myocardial fibrosis. Because of the tendency towards persistent VT attacks and a high risk of sudden death, implantation of an ICD must be considered and should be discussed with the patient at an early stage. A recent international consensus document on sarcoidosis-related arrhythmias provides guidance on which patients should be considered for ICD implantation [34]. In those with a high-grade AV block, an implantation of a permanent pacemaker is indicated [44].

Heart failure owing to cardiac sarcoidosis should always be treated with guideline-directed medical therapy, as described above. Heart transplantation is an option for patients in NYHA functional class IIIB-IV or in those with intractable arrhythmias, with satisfactory outcomes [54]. However, there is a risk of recurrence of the sarcoidosis in the transplanted heart and little is known about long-term morbidity and mortality in this group after heart transplantation [55].

9. Giant cell myocarditis

Giant cell myocarditis (GCM) is a rare inflammatory heart disease of unknown etiology, which is associated with thymoma, inflammatory bowel disease and

other autoimmune disorders [1]. The myocardial inflammation is characterized by widespread infiltration of giant cells along with several other inflammatory cell types that cause myocyte destruction [43]. Giant cells themselves are abnormal cell masses generated by the fusion of several macrophages (**Figure 4C**). Evidence suggests that this phenomenon may arise in response to immune dysregulation mediated by T-lymphocytes [43]. Giant cell myocarditis has been commonly depicted as a rapidly progressive and usually fatal condition for which heart transplantation is the treatment of choice [56]. The disease caught attention in the 1990's when the International Multicenter Giant Cell Myocarditis Study Group reported that 89% of the 63 included patients with the disease either required heart transplantation or died. The median transplant-free survival rate was only 5.5 months [56]. In a later analysis, the overall transplant-free survival at 5 years in patients with giant cell myocarditis was reported to be as low as 10% [57]. However, previous epidemiological studies are confounded by the fact that most patients were diagnosed after heart transplantation or at autopsy.

The initial symptoms of giant cell myocarditis comprise chest pain, palpitations, fatigue, breathlessness and ankle swelling. Individuals with giant cell myocarditis often exhibit advanced heart failure and life-threatening arrhythmias [21]. Endomyocardial biopsy is the gold standard for diagnosis [9]. Cardiac MR and PET/CT are useful for identifying targets for biopsy. The combination of cardiac MR and endomyocardial biopsy has been shown to improve detection rates. When a clinical suspicion remains high despite a negative biopsy, repeat sampling is recommended [1].

Patients who are diagnosed in the early phase of the disease may respond to immunosuppressive treatment, including calcineurin inhibitors (tacrolimus or cyclosporine), an antimetabolite (mycophenolate mofetil or azathioprine) and prednisolone, but an ongoing disease process rapidly damages the heart, which is why heart transplantation often becomes the only realistic treatment option. Owing to the severity of heart failure and the presence of treatment-resistant ventricular arrhythmias, patients with giant cell myocarditis frequently develop multiorgan failure and require durable mechanical support with either a left ventricular or a bi-ventricular assist device as a bridge-to-transplantation [55]. Patients treated with combined immunosuppression have a median survival of 12.3 months from the onset of symptoms, compared to 3.0 months without immunosuppression [58]. Early and aggressive arrhythmia management, including radiofrequency catheter ablation, has been suggested to prolong survival [59]. Early initiation of immunosuppressive therapy also seems to improve outcomes in patients with this aggressive cardiac disease [59].

10. Eosinophilic myocarditis

Eosinophilic myocarditis is a rare and potentially lethal disease characterized by eosinophilic infiltrates in the myocardial tissue (**Figure 4D**). It may occur in association with malignancy, parasite infection, hypersensitivity, and also an idiopathic hyper-eosinophilic syndrome [60, 61]. However, the relative associations between proposed triggers and myocardial eosinophilia remain elusive and, in most cases, the underlying cause remains unknown [1, 60]. The clinical presentation can range from mild symptoms to chronic restrictive cardiomyopathy (Loeffler cardiomyopathy) or acute fulminant myocarditis (also called acute necrotizing eosinophilic myocarditis) [60]. The definite diagnosis of eosinophilic myocarditis can only be achieved with an endomyocardial biopsy, although clinicians often base the diagnosis on laboratory findings and imaging examinations, mainly cardiac MR [1, 9].

In most cases, eosinophilia can be detected in peripheral blood samples and this finding together with cardiac symptoms should always raise suspicions of eosinophilic myocarditis. However, in the early stage of the disease, peripheral eosinophilia may be absent and it may not develop at all in a subgroup of patients. Circulating markers of inflammation and myocardial injury are often increased and natriuretic peptides increase in parallel with the severity of the heart failure syndrome. Normal laboratory tests do not, however, exclude the presence of the disease [60].

The ECG is often abnormal, mainly demonstrating ST-T segment abnormalities, but this is neither sensitive nor specific for eosinophilic myocarditis. The echocardiogram is of pivotal importance with respect to excluding other heart failure etiologies, evaluating left ventricular systolic and diastolic function and monitoring the presence of pericardial effusion. Cardiac MR allows for the identification of edema and diffuse foci of delayed enhancement reflecting myocardial inflammation, necrosis and fibrosis. In stable patients, it is reasonable to perform cardiac MR imaging prior to endomyocardial biopsy, as the former may help to identify focal pathology through late enhancement and guide myocardial tissue sampling. However, in unstable patients an endomyocardial biopsy should be prioritized [60, 62, 63]. Eosinophilic myocarditis, particularly in its fulminant form, is associated with high in-hospital mortality, but owing to the rarity of the disease, no reliable data on mortality rates are available. Its incidence and prevalence are probably under-estimated, as the disease is most usually discovered post-mortem [60].

The treatment and prognosis of eosinophilic myocarditis depends on its etiology. In the acute phase, restriction of physical activity is an important measure. In selected patients, particularly in those with suspected autoreactive etiology and negative virology, early treatment with corticosteroids has resulted in advantageous outcomes [64]. Nevertheless, the evidence supporting corticosteroid therapy is limited, deriving from small, non-randomized studies. Moreover, the initial dosage and treatment duration vary between different reports and, therefore, no evidence-based recommendations can be presented. It is not unreasonable, however, to adjust the steroid dose and treatment duration to the severity of the disease and the primary underlying disorder [60, 62, 64]. The monoclonal antibody benralizumab, which binds to the interleukin-5 receptor on the cell surface and causes apoptosis of eosinophils, has recently been advocated as a promising new therapeutic strategy for eosinophil myocarditis [60].

11. Conclusions

Inflammatory cardiomyopathy refers to a diverse group of disorders in which inflammation of the heart muscle is accompanied by disturbances of cardiac structure and/or function. The diagnosis of these disorders remains challenging despite recent advances in imaging and molecular biology techniques. Together with careful anamnestic enquiry, physical examination and laboratory tests, a comprehensive diagnostic work-up, including both non-invasive and invasive methods, is required to reach a conclusion with respect to identification, management and prognosis. Although cardiac MR and PET/CT represent fundamental non-invasive diagnostic methods, endomyocardial biopsy remains the gold standard. Regular treatment of inflammatory cardiomyopathies is based on the guideline-directed therapy for heart failure and arrhythmias. More targeted therapies, including immunomodulating treatment, can be indicated only when histopathological findings from the endomyocardial biopsy are known. However, owing to a lack of evidence, an individual assessment of each patient is of vital importance for the management of

inflammatory cardiomyopathies. Large prospective multicenter randomized studies are needed to generate evidence-based treatment recommendations in this specific group of patients.

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Conflict of interest

The authors declare no conflict of interest.

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References

- [1] Trachtenberg BH, Hare JM. Inflammatory Cardiomyopathic Syndromes. *Circ Res.* 2017;121(7): 803-18.
- [2] Tschope C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol.* 2021;18(3):169-93.
- [3] Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, et al. Report of the 1995 World Health Organization/ International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. *Circulation.* 1996;93(5):841-2.
- [4] Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J.* 2013;34(33):2636-48, 48a-48d.
- [5] Krejci J, Mlejnek D, Sochorova D, Nemec P. Inflammatory Cardiomyopathy: A Current View on the Pathophysiology, Diagnosis, and Treatment. *Biomed Res Int.* 2016;2016:4087632.
- [6] Ammirati E, Frigerio M, Adler ED, Basso C, Birnie DH, Brambatti M, et al. Management of Acute Myocarditis and Chronic Inflammatory Cardiomyopathy: An Expert Consensus Document. *Circ Heart Fail.* 2020;13(11):e007405.
- [7] Ammirati E, Cipriani M, Bonacina E, Garascia A, Oliva F. [Endomyocardial biopsy should be performed in selected patients with suspected myocarditis]. *G Ital Cardiol (Rome).* 2015;16(10):539-43.
- [8] Ammirati E, Cipriani M, Moro C, Raineri C, Pini D, Sormani P, et al. Clinical Presentation and Outcome in a Contemporary Cohort of Patients With Acute Myocarditis: Multicenter Lombardy Registry. *Circulation.* 2018;138(11):1088-99.
- [9] Elliott P, Arbustini E. The role of endomyocardial biopsy in the management of cardiovascular disease: a commentary on joint AHA/ACC/ESC guidelines. *Heart.* 2009;95(9):759-60.
- [10] Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ, Jr., et al. Myocarditis. A histopathologic definition and classification. *Am J Cardiovasc Pathol.* 1987;1(1):3-14.
- [11] Magnani JW, Danik HJ, Dec GW, Jr., DiSalvo TG. Survival in biopsy-proven myocarditis: a long-term retrospective analysis of the histopathologic, clinical, and hemodynamic predictors. *Am Heart J.* 2006;151(2):463-70.
- [12] Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. *J Am Coll Cardiol.* 2018;72(24):3158-76.
- [13] Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, et al. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. *J Am Coll Cardiol.* 2009;53(17):1475-87.
- [14] Chen W, Jeudy J. Assessment of Myocarditis: Cardiac MR, PET/CT, or PET/MR? *Curr Cardiol Rep.* 2019;21(8):76.
- [15] Calder PC, Dimitriadis G, Newsholme P. Glucose metabolism in lymphoid and inflammatory cells and

tissues. *Curr Opin Clin Nutr Metab Care*. 2007;10(4):531-40.

[16] Nunes MCP, Beaton A, Acquatella H, Bern C, Bolger AF, Echeverria LE, et al. Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management: A Scientific Statement From the American Heart Association. *Circulation*. 2018;138(12):e169-e209.

[17] Dominguez F, Kuhl U, Pieske B, Garcia-Pavia P, Tschope C. Update on Myocarditis and Inflammatory Cardiomyopathy: Reemergence of Endomyocardial Biopsy. *Rev Esp Cardiol (Engl Ed)*. 2016;69(2):178-87.

[18] Kuhl U, Pauschinger M, Noutsias M, Seeberg B, Bock T, Lassner D, et al. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. *Circulation*. 2005;111(7):887-93.

[19] Lieberman EB, Hutchins GM, Herskowitz A, Rose NR, Baughman KL. Clinicopathologic description of myocarditis. *J Am Coll Cardiol*. 1991;18(7):1617-26.

[20] Butta C, Zappia L, Laterra G, Roberto M. Diagnostic and prognostic role of electrocardiogram in acute myocarditis: A comprehensive review. *Ann Noninvasive Electrocardiol*. 2020;25(3).

[21] Ammirati E, Camici PG. Still poor prognosis for patients with giant cell myocarditis in the era of temporary mechanical circulatory supports. *Int J Cardiol*. 2018;253:122-3.

[22] Veronese G, Ammirati E, Cipriani M, Frigerio M. Fulminant myocarditis: Characteristics, treatment, and outcomes. *Anatol J Cardiol*. 2018;19(4):279-86.

[23] Felker GM, Boehmer JP, Hruban RH, Hutchins GM, Kasper EK,

Baughman KL, et al. Echocardiographic findings in fulminant and acute myocarditis. *J Am Coll Cardiol*. 2000;36(1):227-32.

[24] Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, et al. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. *J Am Coll Cardiol*. 2009;53(17):1475-87.

[25] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;18(8):891-975.

[26] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):2117-28.

[27] McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381(21):1995-2008.

[28] Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail*. 2012;5(1):54-62.

[29] Mason JW, O'Connell JB, Herskowitz A, Rose NR, McManus BM, Billingham ME, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. *N Engl J Med*. 1995;333(5):269-75.

- [30] Frustaci A, Chimenti C, Calabrese F, Pieroni M, Thiene G, Maseri A. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. *Circulation*. 2003;107(6):857-63.
- [31] Birnie DH. Cardiac Sarcoidosis. *Semin Respir Crit Care Med*. 2020;41(5):626-40.
- [32] Birnie DH, Nery PB. Debating the Definition and Incidence of Isolated Cardiac Sarcoidosis. *JACC Clin Electrophysiol*. 2020;6(9):1190-1.
- [33] Trivieri MG, Spagnolo P, Birnie D, Liu P, Drake W, Kovacic JC, et al. Challenges in Cardiac and Pulmonary Sarcoidosis: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020;76(16):1878-901.
- [34] Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*. 2014;11(7):1305-23.
- [35] Birnie DH, Sauer WH, Judson MA. Consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart*. 2016;102(6):411-4.
- [36] Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Ylitalo K, et al. Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. *Circulation*. 2015;131(7):624-32.
- [37] Al-Kindi SG, Oliveira GH. Letter by Al-Kindi and Oliveira regarding article "cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study". *Circulation*. 2015;132(17):e211.
- [38] Muchtar E, Blauwet LA, Gertz MA. Restrictive Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. *Circ Res*. 2017;121(7):819-37.
- [39] Rossman MD, Thompson B, Frederick M, Maliarik M, Iannuzzi MC, Rybicki BA, et al. HLA-DRB1*1101: a significant risk factor for sarcoidosis in blacks and whites. *Am J Hum Genet*. 2003;73(4):720-35.
- [40] Rossman MD, Thompson B, Frederick M, Iannuzzi MC, Rybicki BA, Pander JP, et al. HLA and environmental interactions in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2008;25(2):125-32.
- [41] Agostini C, Adami F, Semenzato G. New pathogenetic insights into the sarcoid granuloma. *Curr Opin Rheumatol*. 2000;12(1):71-6.
- [42] Ekstrom K, Lehtonen J, Nordenswan HK, Mayranpaa MI, Raisanen-Sokolowski A, Kandolin R, et al. Sudden death in cardiac sarcoidosis: an analysis of nationwide clinical and cause-of-death registries. *Eur Heart J*. 2019;40(37):3121-8.
- [43] Kandolin R, Lehtonen J, Kupari M. Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. *Circ Arrhythm Electrophysiol*. 2011;4(3):303-9.
- [44] Nordenswan HK, Lehtonen J, Ekstrom K, Kandolin R, Simonen P, Mayranpaa M, et al. Outcome of Cardiac Sarcoidosis Presenting With High-Grade Atrioventricular Block. *Circ Arrhythm Electrophysiol*. 2018;11(8):e006145.
- [45] Mehta D, Lubitz SA, Frankel Z, Wisnivesky JP, Einstein AJ, Goldman M, et al. Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. *Chest*. 2008;133(6):1426-35.

- [46] Skold CM, Larsen FF, Rasmussen E, Pehrsson SK, Eklund AG. Determination of cardiac involvement in sarcoidosis by magnetic resonance imaging and Doppler echocardiography. *J Intern Med.* 2002;252(5):465-71.
- [47] Ekstrom K, Lehtonen J, Hanninen H, Kandolin R, Kivisto S, Kupari M. Magnetic Resonance Imaging as a Predictor of Survival Free of Life-Threatening Arrhythmias and Transplantation in Cardiac Sarcoidosis. *J Am Heart Assoc.* 2016;5(5).
- [48] Kandolin R, Lehtonen J, Graner M, Schildt J, Salmenkivi K, Kivisto SM, et al. Diagnosing isolated cardiac sarcoidosis. *J Intern Med.* 2011;270(5):461-8.
- [49] Ohira H, Birnie DH, Pena E, Bernick J, Mc Ardle B, Leung E, et al. Comparison of (18) F-fluorodeoxyglucose positron emission tomography (FDG PET) and cardiac magnetic resonance (CMR) in corticosteroid-naive patients with conduction system disease due to cardiac sarcoidosis. *Eur J Nucl Med Mol Imaging.* 2016;43(2):259-69.
- [50] Ichinose A, Otani H, Oikawa M, Takase K, Saito H, Shimokawa H, et al. MRI of cardiac sarcoidosis: basal and subepicardial localization of myocardial lesions and their effect on left ventricular function. *AJR Am J Roentgenol.* 2008;191(3):862-9.
- [51] Erthal F, Juneau D, Lim SP, Dwivedi G, Nery PB, Birnie D, et al. Imaging of cardiac sarcoidosis. *Q J Nucl Med Mol Imaging.* 2016;60(3):252-63.
- [52] Bennett MK, Gilotra NA, Harrington C, Rao S, Dunn JM, Freitag TB, et al. Evaluation of the role of endomyocardial biopsy in 851 patients with unexplained heart failure from 2000-2009. *Circ Heart Fail.* 2013;6(4):676-84.
- [53] Ekstrom K, Lehtonen J, Kandolin R, Raisanen-Sokolowski A, Salmenkivi K, Kupari M. Incidence, Risk Factors, and Outcome of Life-Threatening Ventricular Arrhythmias in Giant Cell Myocarditis. *Circ Arrhythm Electrophysiol.* 2016;9(12).
- [54] Toma M, Birnie D. Heart Transplantation for End-Stage Cardiac Sarcoidosis: Increasingly Used With Excellent Results. *Can J Cardiol.* 2018;34(8):956-8.
- [55] Bobbio E, Lingbrant M, Nwaru BI, Hessman E, Lehtonen J, Karason K, et al. Inflammatory cardiomyopathies: short- and long-term outcomes after heart transplantation-a protocol for a systematic review and meta-analysis. *Heart Fail Rev.* 2020;25(3):481-5.
- [56] Cooper LT, Jr., Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis--natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators. *The New England journal of medicine.* 1997;336(26):1860-6.
- [57] Okura Y, Dec GW, Hare JM, Kodama M, Berry GJ, Tazelaar HD, et al. A clinical and histopathologic comparison of cardiac sarcoidosis and idiopathic giant cell myocarditis. *Journal of the American College of Cardiology.* 2003;41(2):322-9.
- [58] Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *Eur Heart J.* 2009;30(16):1995-2002.
- [59] Ekstrom K, Lehtonen J, Kandolin R, Raisanen-Sokolowski A, Salmenkivi K, Kupari M. Long-term outcome and its predictors in giant cell myocarditis. *Eur J Heart Fail.* 2016;18(12):1452-8.
- [60] Brambatti M, Matassini MV, Adler ED, Klingel K, Camici PG,

Ammirati E. Eosinophilic Myocarditis: Characteristics, Treatment, and Outcomes. *J Am Coll Cardiol.* 2017;70(19):2363-75.

[61] Ammirati E, Stucchi M, Brambatti M, Spano F, Bonacina E, Recalcati F, et al. Eosinophilic myocarditis: a paraneoplastic event. *Lancet.* 2015;385(9986):2546.

[62] Kuchynka P, Palecek T, Masek M, Cerny V, Lambert L, Vitkova I, et al. Current Diagnostic and Therapeutic Aspects of Eosinophilic Myocarditis. *BioMed Research International.* 2016;2016:2829583.

[63] Li H, Dai Z, Wang B, Huang W. A case report of eosinophilic myocarditis and a review of the relevant literature. *BMC Cardiovascular Disorders.* 2015;15(1):15.

[64] Yanagisawa T, Inomata T, Watanabe I, Maekawa E, Mizutani T, Shinagawa H, et al. Clinical significance of corticosteroid therapy for eosinophilic myocarditis. *Int Heart J.* 2011;52(2):110-3.